



# Is Phenacetin A Nephrotoxin?

## A Report on Twenty-three Users of the Drug

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■ Numerous reports of chronic renal disease in patients who habitually use phenacetin-containing compounds to excess have aroused considerable controversy over the possible relationship between phenacetin, alone or in combination with other analgesics, and the occurrence of renal damage.

*Between 1961 and 1964, we have seen 23 patients with severe renal failure and a history of prolonged, excessive use of phenacetin-containing compounds. In all instances the clinical and laboratory data were compatible with "phenacetin nephritis" as described in Europe and Australia and recently in the United States and Canada. This report evaluates the findings in the 23 cases and cautions against the use of phenacetin, particularly in patients with impaired renal function.*

RENAL DISEASE attributed to ingestion of phenacetin has been extensively reported in Europe and Australia.\* Reports of similar cases in this country<sup>25-27,29,30</sup> and Canada<sup>19</sup> have been infrequent, leading to the impression that nephropathy resulting from overuse of phenacetin (acetophenetidin) is uncommon in this hemisphere.<sup>31</sup> Recent experience by us and others,<sup>5-7,25,32</sup> however, is rapidly contradicting this impression. During the past three years, we have seen severe renal insufficiency in association with a history of prolonged, excessive use of phenacetin-containing compounds in 23 patients referred to the

Renal Service of the University of California Medical Center for evaluation.† The data on the patients were carefully reviewed to exclude other possible causes of deterioration of renal function. Two of the 23 cases were considered doubtful because excessive ingestion of phenacetin could not be established unequivocally. The patients were included in our series, however, because the clinical and laboratory findings (and, in one, postmortem evidence of bilateral papillary necrosis) were typical of "phenacetin nephritis."

The pertinent findings in the 23 cases, although not conclusive, provide strong circumstantial evi-

\*References Nos. 1-4, 14, 16, 21, 23, 24, 28, 33, 34.

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Submitted July 14, 1964.

†Our series does not include eight cases of papillary necrosis thought to be caused by excessive ingestion of phenacetin which are being reported by Dr. Donald R. Smith of the Division of Urology, University of California Medical Center.<sup>32</sup>

dence to support belief that phenacetin or its metabolites were instrumental in the pathogenesis of the renal lesions in these patients.

### Data on Cases

The clinical and laboratory findings in the 23 cases are summarized in Table 1. The patients, eighteen women and five men, ranged in age from 40 to 70 years. All had taken phenacetin-containing compounds to excess for at least two years; in half the group the duration of analgesic abuse was ten years or more. The total dosage of phenacetin was difficult to determine, since in general the patients were evasive when questioned about their drug intake. Most, however, admitted to taking analgesics daily and in large amounts. Anacin,<sup>†</sup> a combination of phenacetin (160 mg per tablet), aspirin and caffeine, was the most popular preparation, although other phenacetin-containing mixtures were also used. In all cases the drugs were taken for relief of pain, chiefly headache; in one case, that of a patient with rheumatoid arthritis, a phenacetin-containing preparation had been prescribed.

In the majority of patients the presenting symptom was nonspecific, such as indigestion or abdominal pain, pain in the flank or back or edema of the face and legs. Many of the patients also complained of episodes of nausea and vomiting over long periods (six months to two years). Hypertension was present in ten cases, but was mild in degree except in two patients (Cases 6 and 12) who also had diabetes mellitus. All but one patient had severe anemia (hematocrit, 21 to 33 per cent). Neurological signs (hyperactive reflexes, positive plantar extensor response, decreased vibration sense, decreased position sensation, convulsion, somnolence, disorientation, or agitation and confusion) were noted in seven cases. Two patients (Cases 11 and 20) were admitted to the hospital in a semicomatose state. Seven were considered psychoneurotic. Gastric or duodenal ulcers were found in four patients (Cases 2, 7, 9 and 17); Kincaid-Smith<sup>18</sup> has similarly reported a high incidence of ulcer in phenacetin users.

Kidney function was severely impaired in all but two patients (Cases 10 and 21), as evidenced by nonprotein nitrogen levels ranging from 46 to 225 mg per 100 ml, serum creatinine concentrations ranging from 4.0 to 15.2 mg per 100 ml and creatinine clearances ranging from 50 ml per minute to as low as 2 ml per minute. Except for inability to excrete concentrated urine, the urinary abnormalities were minimal, consisting in most cases of slight proteinuria (0 to 1+), occasional red and white blood cells, and rare casts (usually hyaline). Urine cultures, performed on two to nine occasions in 22

cases, were persistently negative in 11; and in the other 11 cases urinary infections appeared late in the course of disease.

Serum methemoglobin and sulfhemoglobin levels, determined in six cases, were positive in two. One other patient (Case 13), who also claimed to have taken no analgesics for a long time, had the slatey blue skin often associated with prolonged use of phenacetin.<sup>4,5</sup>

X-ray examination, either by plain film, intravenous urogram, retrograde pyelogram or tomogram, was performed in all cases, although in one (Case 11) the kidneys could not be visualized because of massive ascites. In five patients, the kidneys were normal in size, in eleven both kidneys were smaller than normal, and in four one kidney was decreased in size. Roentgenological evidence of papillary necrosis was found bilaterally in eight cases and unilaterally in four. In one of the patients in whose one functioning kidney papillary necrosis was found (Case 14), obstruction of the ureter by a sloughed papilla was thought to be the cause of acute renal insufficiency. After the patient discontinued taking Bromo-Seltzer®, renal function returned to normal (creatinine clearance of 109 ml per minute). Roentgenographic examination during a follow-up period of approximately two years has shown no further evidence of papillary necrosis and the *Pseudomonas aeruginosa* infection has cleared. One additional patient (Case 23) had undergone nephrectomy previously; the remaining kidney, which was hypertrophied, showed evidence of papillary necrosis.

Renal biopsy, performed in four cases, showed interstitial fibrosis in three. In the remaining cases renal biopsy was contraindicated by the presence of a bleeding tendency, hypertension, severely impaired renal function or small kidneys. Three of the 23 patients were examined at autopsy. The results confirmed the biopsy finding of interstitial nephritis in one (Case 7) and showed the presence of renal papillary necrosis bilaterally in addition to interstitial nephritis in the others (Cases 20 and 22). The pathological findings will be described in detail in a subsequent report.

The findings in two patients (Cases 11 and 12) were of particular interest. The patients, a married couple (no consanguinity), were admitted to the hospital within a month of each other. Both had severe azotemia, associated with convulsions and disorientation. The wife was in a semicomatose state at the time of admission. On careful questioning, both admitted to taking A.P.C. (aspirin-phenacetin-caffeine) tablets in large quantities for years. They kept the tablets in a bowl in the living room and took them like candy. Neither was aware of having renal disease, although both had experienced several episodes of urinary frequency and nocturia during

<sup>†</sup>Whitehall Laboratories, manufacturers of Anacin, informed us that phenacetin was removed from the compound in January 1963.

the six months before admission to the hospital. The husband was hypertensive and had diabetes mellitus, which was controlled by diet and 20 units of NPH insulin daily; he died of renal failure shortly after being discharged. At present, the wife has a creatinine clearance of 9 ml per minute, requiring stringent dietary, fluid and salt regulation.<sup>13</sup>

## Discussion

The clinical and laboratory findings in the present series were similar to those described in previous

reports of renal disease in association with excessive use of analgesics. As in the cases here described, the presenting complaint is usually nonspecific. Chronic headache is the outstanding symptom, and often is the clue to a history of prolonged, excessive use of analgesics. Many compounds for headache and other types of pain contain phenacetin, and this drug has been consistently implicated in such cases. The typical picture consists of severe anemia, absence of hypertension (or only mild hypertension), and serious impairment of renal function, with re-

TABLE 1.—Clinical and Laboratory Data in 20 Cases of Suspected Phenacetin Nephritis

Case No.	Age and Sex	Phenacetin Intake			Blood Pressure (mm mercury)	Hematocrit (per cent)	Ccr (ml/min*)	Urine		Roentgenographic Findings			
		Estimated Cumulative Dose (kg)	Duration (years)	Reason for Taking				Protein	Culture	Kidney Size r	Kidney Size l	Papillary Necrosis r	Papillary Necrosis l
1	41 F	5.8-8.3	5	Headache	150/100	27	15	0.1+	Negative	<	<	0	0
2	48 F	7.0	10	Headache	115/65	26	25	0	Negative	<	<	+	+
3	51 F	1.5	2	Headache	120/80	27	7	0.2+	<i>Aerobacter</i>	<	<	0	0
4	40 F	3.7	8	Headache, backache	150/110	21	11	1+	<i>Enterococci, Aerobacter</i>	N	N	0	0
5	61 F	3.6	10	Headache, rectal pain	110/70	23	12	1+	Negative	N	<	+	+
6	51 F	10.0	7	Headache	215/120	33	17	1+	Negative	<	<	0	0
7	70 F	2.2	10	Ophthalmic neuralgia	160/110	31	7	0.1+	<i>E. coli, Enterococci</i>	N	N	0	0
8	63 F	8.3	10	Headache	150/80	28	6	1+	Negative	<	<	+	0
9	50 F	2.5	5	Rheumatoid arthritis	150/100	28	4	0.1+	.....	N	N	0	0
10	42 F	?	Many	Headache, backache	140/90	42	50	0.1+	Negative	<	<	+	+
11†	62 F	?	6	Headache	160/100	23	2	1+	<i>E. coli</i>	?	?	?	?
12	62 M	8.0-10.0	25	Headache, abdominal pain	210/90	25	5	1+	<i>Staph. albus</i>	<	<	+	+
13	47 M	By the bottle	25	Headache	110/60	30	6	0.1+	Negative	<	<	0	0
14	45 M	2.5	20	Epigastric pain	120/80	25	3	0.1+	<i>Ps. aeruginosa</i>	>	<	+	0
15	67 F	6.2	17	Headache	160/80	35	29	1+	Negative	N	N	0	0
16	28 M	?	6	Headache	150/100	28	10	1.2+	Negative	>	>	+	+
17	53 F	4.7	8	Headache	145/95	38	34	0.1+	<i>E. coli</i>	<	N	?	0
18	46 F	?	3	Headache	160/80	35	5	1+	Negative	<	<	0	0
19	38 F	11.0	19	Leg pain (ulcers)	140/90	33	29	1+	<i>E. coli</i>	<	<	+	+
20	71 F	2.3	2	Headache	110/50	29	5	2+	<i>Aerobacter, E. coli</i>	N	N	+	+
21	50 F	17.5	15	Gouty arthritis	120/80	40	48	1+	Negative	<	N	0	+
Doubtful Cases													
22	65 F	?	5	Rheumatoid arthritis	155/80	21	8	4+	<i>Enterococci, E. coli</i>	<	<	+	+
23‡	48 M	0.5	2	Abdominal pain	130/80	29	14	1+	<i>Proteus</i>	-	>	-	+

\*Corrected to a body surface area of 1.73 square meters.

†Patient had massive ascites.

‡Right kidney had been removed previously.

### Explanation of Abbreviations and Symbols

Ccr=Creatinine clearance.

r=Right kidney; l=left kidney.

<=Smaller than normal.

>=Larger than normal.

N=Normal.

markedly slight urinary abnormalities.<sup>27,28</sup> The kidneys are usually either of normal size or shrunken. The renal lesion consists of interstitial nephritis, often in combination with papillary necrosis.<sup>11,12,15,19</sup>

After oral ingestion the drug is absorbed completely from the upper part of the gastrointestinal tract. A maximum plasma level is reached within one or two hours. A fraction of the ingested drug is bound to plasma protein; the remainder (approximately 99.8 per cent) is metabolized and converted to acetyl-p-aminophenol, some of which is conjugated with glucuronic acid or sulfate ion. Less than 0.1 per cent is changed to p-phenetidin by deacetylation. In 24 hours, 3.5 per cent of the ingested dose is found in the urine in the form of free aminophenol and 74 per cent in the form of conjugated N-acetyl-p-aminophenol.\*<sup>10</sup>

Toxic properties other than nephrotoxicity have been well established. One of the major toxic effects of phenacetin is the conversion of hemoglobin to methemoglobin and sulfhemoglobin within the red blood cells,<sup>8</sup> with consequent reduction in erythrocyte survival time. The ingestion of phenacetin can also cause intravascular hemolysis,<sup>8,17</sup> leading to severe anemia. Persons with an inherited deficiency of glucose-6-phosphate dehydrogenase are said to be particularly susceptible to this type of hemolytic anemia.<sup>9</sup> The formation of methemoglobin and sulfhemoglobin and the decreased erythrocyte survival time may cause a reduction in the amount of hemoglobin available for oxygen transportation, leading to chronic anoxemia. The relative hypoxia in combination with the direct depressant action of high concentrations of phenacetin on the heart, circulation and central nervous system<sup>7,10</sup> may lead to vascular collapse and shock. The symptoms of central nervous system disturbance include severe headache, irritability, nervousness, insomnia, inability to concentrate and delirium, which may be followed by depression, stupor and even coma. Paradoxically, phenacetin has the ability to relieve the headaches it causes. The headaches, however, usually become more severe when phenacetin is withdrawn, causing the patient to seek relief in increased doses of the drug.

Methemoglobin and sulfhemoglobin disappear from the blood in several days and in two to three months, respectively, after withdrawal of phenacetin,<sup>4</sup> which might account for negative findings in four of the six cases in the present series in which the plasma methemoglobin and sulfhemoglobin levels were determined. These substances are responsible for the reversible slatey cyanosis of skin, mucosa and fingernails seen in association with excessive

ingestion of phenacetin and as noted in one of the patients (Case 13) in the series.

The cause and mechanism of the nephropathic change is not known. Circumstantial evidence, however, suggests a cause-and-effect relationship between phenacetin addiction and renal damage. Several mechanisms have been suggested including the toxic effects of the breakdown products of phenacetin, chronic renal hypoxia resulting from decreased erythrocyte survival time, excretion of abnormal forms of hemoglobin, and a hypersensitivity reaction.<sup>28</sup> Chemical toxicity has also been suggested. For example, acetic-4-chloranilide, a contaminant produced in the manufacture of phenacetin, may make the kidney susceptible to bacterial invasion, with subsequent inflammatory changes.<sup>16</sup> Gilman<sup>9</sup> postulated that the combination of phenacetin and aspirin or caffeine might act synergistically to produce renal damage, or that aspirin alone might be the toxic agent. Aspirin, in large doses, has been used for many years at the U.C. Medical Center, San Francisco, for the prolonged treatment of rheumatoid diseases. Whereas it can cause renal irritation and hematuria, we know of no instance in which it has led to serious permanent renal injury.

Despite severe renal failure the urinary abnormalities in many of the patients in the present series were slight. They were typical of those found in interstitial nephritis,<sup>19,28</sup> in contrast to active renal papillitis, which is characterized by hematuria (often gross) and varying degrees of pyuria, probably depending at least in part on complicating infection. We were impressed that the interstitial nephritis following phenacetin abuse may lead to dichotomy of renal function with relatively greater depression of tubular than glomerular function.

The finding of urinary tract infection in nine of the patients late in the course of disease requires consideration. Some investigators<sup>20,27</sup> have suggested that bacterial infection is a late complication that further compromises renal function and may be related to the sloughing of papilla, perhaps by diminishing the precarious supply of blood to this area. In eleven of the patients, however, no evidence of past or present infection of the urinary tract could be found either by history or by repeated urine cultures and quantitative bacteriologic counts. In these patients, at least, the "wastebasket" diagnosis of chronic pyelonephritis is not warranted. In addition, some of the patients in whom urinary tract infections developed recovered promptly following sterilization of the urine by administration of antibiotics, whereas such treatment is usually ineffective in patients with chronic pyelonephritis. Pyelonephritis associated with papillary necrosis has been reported as a complication in nephrocalcinosis, sickle cell anemia and diabetes mellitus.<sup>22</sup> One wonders whether

\*N-acetyl-p-aminophenol is now being substituted for phenacetin in some drug compounds. Whether it is nephrotoxic has not yet been established.

the possibility that such patients may have increased susceptibility to nephrotoxicity from phenacetin was considered in the reported cases.

A diagnosis of chronic glomerulonephritis with renal insufficiency in the patients in the present series also appeared to be ruled out by the absence of the pronounced urinary abnormalities and hypertension so characteristic of that condition. In five cases the presence of glomerulonephritis was definitely excluded by either biopsy or autopsy findings.

All the patients were cautioned about the use of phenacetin-containing drugs. In some cases, analgesics had been discontinued some time previously on the advice of the referring physicians. In our experience, after withdrawal of phenacetin-containing compounds the renal lesion tended to stabilize and further papillitis and renal damage did not occur. Since papillary necrosis can develop before parenchymal damage is severe, discontinuation of the drug may be followed by recovery (Case 14).

Although conclusive proof is lacking, circumstantial evidence strongly suggests that phenacetin was an important factor in the occurrence of the renal lesions in the patients in this series. Unfortunately animal studies on phenacetin toxicity have not yielded conclusive evidence applicable to the problem of nephrotoxicity in man. Until the mechanism leading to renal damage of this type can be firmly established, the use of phenacetin-containing drugs should be avoided, especially in patients with known renal impairment.

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